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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/663,577 | 09/16/2003 | Robert G. Dennis | UOM 0294 PUS | 4495 |

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| EXAMINER | |
|---|---|
| GOUGH, TIFFANY MAUREEN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1651 | |

DATE MAILED: 03/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/663,577 | DENNIS ET AL. | |
| | Examiner | Art Unit | |
| | Tiffany M. Gough | 1651 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 12-11-2003
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1,17, and 32 and their dependents are confusing because they simultaneously require a substrate and then detachment from the substrate.

The claims are also rejected because it is unclear which claim-required substrate would be considered a scaffold and which would not. The terms, "scaffold-free substrate" and "in the absence of a scaffold" are indefinite. A clear definition of what applicant means by scaffold in regards to the invention should be provided.

The function of the "anchors" in claims 9 and 10 is unclear. It appears that the anchors may actually be serving as a scaffold-like structure, enabling the cells to grow around the anchors allowing cell layers to form and enabling ingrowth of tissue. One skilled in the art may be led to consider the claimed "anchors" as a "scaffold" in regards to the vagueness of the word scaffold used in applicants invention. Furthermore, the spatial relationship of the anchors appears to be essential for the growth of cells in the

invention and should be clearly defined. Therefore, claims 9-11,22-24 are rejected under 35 U.S.C 112, second paragraph.

Applicant claims a "suitable recipient" in claim 30. It is unclear who/what a suitable recipient would be.

Applicant's use of the phrase, "three-dimensional" is a bit confusing throughout the invention. Cells in themselves are three-dimensional, but in claim 32 applicant claims a "monolayer detaching from a substrate to form a three-dimensional muscle construct." Claim 32 in itself is confusing and indefinite along with applicant's use of the phrase "three-dimensional."

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5,8,15,17-19,32,33,34, 37 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Malette et al (U.S Patent 4,605,623).

Applicant claims a system and method for forming a cardiac muscle construct comprising a scaffold-free substrate and self-organizing cardiac cells provided on claimed substrate which allow confluent growth of the cells and detachment to form a three-dimensional muscle construct. The cardiac cells include cardiac myocytes and fibroblasts which are spontaneously contractile and are substantially cylindrical.

Malette et al teach a spontaneously contracting three-dimensional cardiac muscle construct grown in absence of a scaffold. The muscle construct includes myocytes and fibroblasts. Malette et al teach growing mycocytes on chitosan plates. Myotubes were formed between two and three days and contraction was seen between four to five days. The cells beat in unison with underlying cells as functional three-dimensional cardiac tissue. Malette et also also mixed cultures of myocytes and fibroblasts (See columns 3 and 4).

Claims 1-9,12,13,15,17-22,25,26 and 32-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Zimmermann et al. (Biotechnology & Bioengineering, 2000).

Applicant claims a system and method for forming a cardiac muscle construct comprising a scaffold-free laminin coated substrate and self-organizing cardiac cells provided on claimed substrate which allow confluent growth of the cells and detachment to form a three-dimensional muscle construct. The system comprises at least two laminin coated silk suture anchors secured to the substrate in spaced relations allowing some of the cardiac cells to attach to the anchors. The cardiac cells include cardiac myocytes and fibroblasts, are spontaneously contractile, and are responsive to electrical and chemical stimuli.

Zimmermann et al also teach spontaneously contracting three-dimensional cardiac muscle construct grown in absence of a scaffold. Their technique allows cardiac myocytes to form in vitro as a planar biconcaval matrix anchored at both sides.

Zimmermann et al teach growing the cells in culture dishes containing a substrate and a set of Velcro-coated silicone tubes to function as anchors (see abstract). Their construct was electrically stimulated with rectangular pulses via two wire electrodes. They also subjected their construct to calcium and isoprenaline, which exhibited a response and in return reduced the effects as seen by isoprenaline by carbachol (see p. 107,109-111 (Zimmermann, Biotechnology and Bioengineering, 2000).

Claims 1-9,12,,15,17-22,25 and 32-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Zimmermann et al. (Circulation Research Feb. 8, 2002).

Applicant claims a system and method for forming a cardiac muscle construct comprising a scaffold-free laminin coated substrate and self-organizing cardiac cells provided on claimed substrate which allow confluent growth of the cells and detachment to form a three-dimensional muscle construct. The system comprises at least two laminin coated silk suture anchors secured to the substrate in spaced relations allowing some of the cardiac cells to attach to the anchors. The cardiac cells include cardiac myocytes and fibroblasts, are spontaneously contractile, are responsive to electrical and chemical stimuli and are substantially cylindrical.

Zimmermann et al teach a cardiac composition containing myocytes and fibroblasts (p.225 last paragraph), which is grown as circular molds on a substrate containing laminin. The cells are self-organizing and form three-dimensional ring-shaped EHT's, which display characteristics of differentiated myocardium such as adherens and gap junctions (see abstract). Cylinders were placed on the substrate as

an "anchor" system for which the cells could grow around (p.224). The cells were responsive to electrical stimulation (p.227 last paragraph) and chemical stimulation such as isoprenaline (p. 228 in vitro applications paragraph).

Claims 1-5,7-9,12,17-19,21,25,32-34,36,38,39 are rejected under 35 U.S.C. 102(b) as being anticipated by Akins et al (Tissue Engineering, vol 5, p.103-118, 1999)

Applicant claims a system and method for forming a cardiac muscle construct comprising a scaffold-free laminin coated substrate and self-organizing cardiac cells provided on claimed substrate which allow confluent growth of the cells and detachment to form a three-dimensional muscle construct. The system comprises at least two laminin coated silk suture anchors secured to the substrate in spaced relations allowing some of the cardiac cells to attach to the anchors. The cardiac cells include cardiac myocytes and fibroblasts, are spontaneously contractile, are responsive to chemical stimuli, are substantially cylindrical and form gap and adherin junctions between the cardiac myocytes..

Akins et al teach a spontaneously contracting three-dimensional cardiac muscle construct grown in absence of a scaffold. Akins et al teach a construct grown on polystyrene culture plates, polystyrene microcarrier beads as well as oriented collagen fibers. They observed cells in a monolayer and three-dimensional culture of myocytes and fibroblast when allowed to grow on fibronectin-coated, polystyrene surfaces. Akins et al also teach cells grown in bioreactors and polystyrene beads. The cells exhibit spontaneous and rhythmical contractions.(p.103-113). They also observed cellular

junctions such as fascia adherins junctions and gap junctions between the cardiac myocytes (p.113). Akins et al assess contractilbility by exposing the cells to propanolol. Propanolol caused a decrease in beat frequency, however eliciting a response to the chemical stimuli (p.108, *contractile function* paragraph)

Claims 1-3,5,6,12,17,18,20,25,32,34,35,39 are rejected under 35 U.S.C. 102(b) as being anticipated by Shimizu (Igaku no Ayumi, 2000,vol 195,p.203-204, see translated document p.2-5)

Applicant claims a system and method for forming a cardiac muscle construct comprising a scaffold-free laminin coated substrate and self-organizing cardiac cells provided on claimed substrate which allow confluent growth of the cells and detachment to form a three-dimensional muscle construct. The cardiac cells include cardiac myocytes and are spontaneously contractile, are responsive to electrical stimuli, are substantially cylindrical and form gap junctions between the cardiac myocytes.

Shimizu teaches cardiac myocyte cell sheets and three-dimensional structures which spontaneously contract, retain intercellular coupling and orientation, were peeled from a substrate, transferred and further multiply layering the cell sheets to form a three-dimensional sheet which also exhibited gap junctions between the sheets and pulsation. The three-dimensional structure was proven to pulse in snychrony by electrically stimulating one side of the cell sheet (See pg's. 3-5 of translated document).

Claims 1-3,5,6,12,17,18,20,25,30,32,34,35,39 are rejected under 35 U.S.C. 102(a) as being anticipated by Shimizu et al (Biomaterials, 7/2003, vol.24, p.2309-2316.)

Applicant claims a system and method for forming a cardiac muscle construct comprising a scaffold-free laminin coated substrate and self-organizing cardiac cells provided on claimed substrate which allow confluent growth of the cells and detachment to form a three-dimensional muscle construct. The cardiac cells include cardiac myocytes and are spontaneously contractile, are responsive to electrical stimuli, are substantially cylindrical and form gap junctions between the cardiac myocytes. Applicant further claims implanting the cardiac muscle construct into a suitable recipient.

Shimizu et al teach growing confluent myocardial cells on a substrate, on which they observed cell-to-cell junctions such as gap junctions, desmosomes and intercalated disks (see pg's.2309-2315 and 2312 last paragraph, continued to 2313). These junctions were confirmed by electrical stimulation applied to the monolayers. (p.2312-2313). The monolayers were further detached from the substrate to form a 3-D structure, which is further transplanted into rats (p.2313).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-27,29 and 32- 40 are rejected under 35 U.S.C. 103(a) as being obvious over Malette (U.S. Patent 4605,623) or Zimmermann (Biotechnology and Bioengineering, 2000) and (Circulation Research Feb. 8, 2002) or Akins (Tissue Engineering, vol 5, p.103-118, 1999) or Shimizu (Igaku no Ayumi, 2000,vol 195,p.203-204) and (Biomaterials, 7/2003, vol.24, p.2309-2316.) in view of Dennis et al (U.S Patent 6,207,451 B1)

Applicant claims a system and method for forming a cardiac muscle construct comprising a scaffold-free laminin coated substrate (0.4-2.0 ug/cm2) and self-organizing cardiac cells provided on claimed substrate which allow confluent growth of the cells and detachment to form a three-dimensional muscle construct. The system comprises at least two laminin coated silk suture anchors secured to the substrate in spaced relations allowing some of the cardiac cells to attach to the anchors. The cardiac cells include cardiac myocytes and fibroblasts, are spontaneously contractile, are responsive to electrical and chemical stimuli and are substantially cylindrical. The system further comprises skeletal muscle cells cultured in combination with the cardiac cells.

As discussed above, each of Malette, Zimmermann, Akins, etc. disclose the production of cardiac cells on a scaffold-free substrate.

Dennis et al teach mammalian muscle construct and method of forming the construct encompassing the claimed embodiments of claims 1-27,32-36 and 40 in the application under examination.

Dennis et al do not teach a cardiac muscle construct specifically and laminin in the amount of "about 0.4-2.0 μg/cm2". However, it would have been obvious to one of ordinary skill in the art at the time of the invention to also use cardiac cells, as disclosed by Malette, etc., in the claimed invention because Dennis et al teach that the myogenic precursor cells used are any cell which can be used to develop a particular tissue of interest. They also teach that myogenic precursor cells are any cell, which can develop into skeletal, smooth or cardiac muscle tissue and includes myocytes and fibroblasts in his discussion of myogenic precursor cells. With regards to the laminin concentration, Dennis et al do teach 0.5-1.0 and 0.3-1.5 μg/cm2, which to one of ordinary skill in the art is "about 0.4-2.0 μg/cm2". In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed.Cir. 1990) (The prior art taught carbon monoxide concentrations of "about 1-5%" while the claim was limited to "more than 5%." The court held that "about 1-5%" allowed for concentrations slightly above 5% thus the ranges overlapped. See MPEP 2144.05

One of ordinary skill in the art, given what is known in the art at the time the invention was made, would have a reasonable expectation of success to form a functional cardiac muscle construct using the mammalian muscle construct and anchor system claimed. Therefore, it would have been obvious to perform the reaction containing the claimed components and conditions as a matter of optimization of these result effective variables.

Claims 1-29 and 32-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malette, Zimmermann, Akins, and Shimizu in view of Dennis et al (U.S. Patent 6,207,451 B1) as applied to claims 1-27,29,32-37 and 40 above, and further in view of Dennis et al (U.S. Patent 6,303,286)

Applicant teaches a method of forming a cardiac muscle construct as previously described, further comprising measuring a functional property of the construct and using the property as feedback to control the formation of the cardiac muscle construct.

Dennis et al (U.S. Patent 6,303,286) teach a system and method for adaptively controlling a muscle tissue specimen in order to emulate its in vivo environment. They teach a desire to promote and control the development of constructs and therefore develop a system and method for integrating and applying multiple stimuli. The system continuously monitors the response of the muscle tissue to stimulation based on an initial control signal, generating a response based on stimulation, and therefore modifying the initial control signal based on the response signal to obtain a final control signal wherein the final signal is used to elicit a desired response from the muscle tissue. They teach that the system may be used for all types of muscle tissue and for tissue of different geometries, specifically mentioning cardiac muscle tissue. (See column 7, first paragraph). Dennis et al teach (U.S. Patent 6,303,286) that it provides integrated, adaptive control of the mechanical and electrical environment of a tissue to promote tissue growth and differentiation (See column 6, paragraph 4.)

Dennis et al (6,303,286) do not teach the method of forming the cardiac muscle construct as claimed by applicant. However, it would have been obvious to apply this system and method of measuring a functional property of the cardiac muscle construct as claimed by applicant, made obvious by Malette etc. in view of Dennis (6,207,451 B1), as discussed above, because Dennis et al (U.S. Patent 6,303,286) specifically teach that the system could be modified to accommodate cardiac muscle tissue and also co-culture systems such as myoblast/fibroblast etc (see column 7, paragraph2) and is advantageous to control the formation of muscle constructs. Therefore, one of ordinary skill in the art would have a reasonable expectation of success to measure a functional property of a cardiac muscle construct and use as feedback to control the growth of the claimed construct.

Claims 1-27 and 29-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malette, Zimmermann, Akins, and Shimizu in view of Dennis et al (U.S. Patent 6,207,451 B1) as applied to claims 1-27,29,32-37 and 40 above, and further in view of Dennis et al (U.S. PG Pub Doc US2001/0049138 A1)

Applicant claims a method for forming a cardiac muscle construct comprising a scaffold-free substrate and self-organizing cardiac cells provided on claimed substrate which allow confluent growth of the cells and detachment to form a three-dimensional muscle construct, further including wrapping an acellularized aorta with a layer of cardiac cells.

Dennis et al (U.S. PG Pub Doc US2001/0049138 A1) teach a method for chemically acellularizing a tissue sample, which can be used for tissue engineering, more specifically tissue grafting and nerve grafting.

Dennis et al teach a three-dimensional mammalian muscle construct more specifically skeletal muscle construct, grown on a scaffold-free substrate (6,207,451 B1). Dennis et al (U.S. Patent 6,207,451 B1) teach that the myogenic precursor cells used are any cell which can be used to develop a particular tissue of interest. They also teach that myogenic precursor cells are any cell, which can develop into skeletal, smooth or cardiac muscle tissue and includes myocytes and fibroblasts in his discussion of myogenic precursor cells.

Dennis et al do not teach wrapping an acelluriazed aorta with a layer of cardiac cells. However, it would have been obvious at the time the invention was made to use cardiac cells in the mammalian muscle construct as taught by Malette, etc. in view of Dennis et al (U.S. Patent 6,207,451 B1) as discussed above, because of what is taught about precursor cells and cardiac cells with regards to their invention and to use this cardiac muscle construct for the purpose of tissue repair, engineering ventricles, and nerves given what is known in the art regarding in vivo tissue engineering and repair. Dennis et al teach a method for acellularizing a biological tissue sample for the purpose of surgical repair and grafting. Although they teach peripheral nerve grafting, one would have a reasonable expectation of success and thus be motivated to use a cardiac muscle construct to construct an engineered ventricle.

Thus the claimed invention as a whole is prima facie obvious over the prior art.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tiffany M. Gough whose telephone number is 571-272-0697. The examiner can normally be reached on M-F 8-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tmg

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PRIMARY EXAMINER